IN THE DRAWINGS

Please replace Fig. 2 with the replacement figure provided herewith. A marked-up copy of figure 2 is also attached.

REMARKS

The present invention relates to compositions and methods for use in the diagnosis of subclinical atherosclerosis.

Despite advances in treating coronary heart disease (CHD), a large number of CHD victims die suddenly without prior symptoms. A recent consensus document suggests that available screening and diagnostic methods are insufficient to identify high-risk CHD patients before the first event occurs, and calls for screening of all asymptomatic men 45-75 years of age and asymptomatic women 55-75 years of age in order to detect and treat those with subclinical atherosclerosis. Naghavi *et al.*, *Am. J. Cardiol.* 98:2H-15H, 2006.

The present invention relates to methods and compositions for identifying subjects at an increased risk for subclinical atherosclerosis. These methods comprise performing an assay that detects monocyte chemoattractant protein-1 ("MCP-1") in a sample from the subject, and correlating the results of that assay to the subject's risk of subclinical atherosclerosis. In various dependent claims, the methods can further comprise the use of one or more additional risk factors in combination with the MCP-1 assay result to assess the subject's risk.

By the present submission, claims 1-31 and 37-39 and 42 are cancelled, and claims 32-34, 40, and 44 are amended herein solely to enhance the Examiner's understanding of the claimed subject matter. The amendments do not alter the scope of the claims and raise no issue of new matter.

Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

1. Sequence Listing

A Sequence Listing has been provided herewith along with a computer readable disk and an appropriate certification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

2. Information Disclosure Statement

Replacement SB08 sheets corrected as suggested by the Examiner are attached herewith. Applicants also attach herewith a new Information Disclosure Statement with SB08 sheets and copies of references.

3. Drawings

The Examiner objects to Fig. 2 of the specification because it is allegedly "missing lines for x- and y- axis." Office Action, page 7. Applicants are not aware of any requirement for such axes on a drawing such as depicted in Fig. 2. Nevertheless, Applicants submit herewith a drawing with the requested axis lines and a marked-up copy showing the addition.

4. Specification

The Examiner has requested amendment of the Abstract (paragraph [0262]) to reflect the subject matter of the claims currently undergoing examination. Applicants have amended the specification accordingly. The amendment raises no issue of new matter.

The Examiner has also requested that certain trademarks used in paragraph [0224] be capitalized and accompanied by generic terminology. Applicants thank the Examiner for the careful reading of the specification, and have amended the specification accordingly. Appellants have also amended paragraph [0234] with regard to certain other trademarks used in that paragraph. These amendments raise no issue of new matter.

5. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 32-44 as allegedly failing to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Independent claim 32 reads as follows, with all other claims depending from this claim:

> A method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising
>
> performing an assay that detects monocyte chemoattractant protein-1 on a blood sample from said subject to provide a monocyte chemoattractant protein-1 assay result; and

correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.

The Examiner takes the position that written description is lacking since "the claims are not limited as to the number of markers." Office Action, page 10. In this regard, the Examiner notes that the claims could encompass other markers that are recited in the specification, and that if 216 other markers are included "there are at least more than $2x10^{216}$ different panels that can be made... [h]owever, the specification fails to provide specific panel of MCP-1 and additional marker combinations, which can be used to diagnose atherosclerosis in a subject." Office Action, page 14.[1]

To the best that Applicants understand this position, it appears that the Examiner objects to the use of "comprising" in the claims, which opens to additional elements, including the addition of additional markers or other risk factors. Applicants respectfully submit that this is always true of claims written in "comprising" form, which never exclude additional unrecited elements or method steps, and so are always open to a literally infinite number of theoretical modifications and variations. The fact that the claims are written in this open form cannot form the basis for a rejection under the written description requirement.

Moreover, Applicants respectfully submit that the Examiner's focus on numbers in this fashion, along with several of the Examiner's other comments in the rejection, indicate a failure to consider the claimed invention with the level of knowledge available in the art. As such, the Examiner's comments throughout the rejection do not fairly reflect what the specification reasonably conveys to the skilled artisan.

For example, the Examiner asserts that "MCP-1 does not possess one of the important features of diagnostic markers as MCP-1 has been implicated in the pathogenesis of a variety of diseases... [and so] lacks specificity. Office Action, page 12. The Examiner also implies that MCP-1, which the present specification demonstrates is

[1] Applicants note that the Examiner's calculation is incorrect. The number of possible combinations of *n* items is 2^n-1, not $2x10^n$. One can readily confirm this by considering the example where n=2. Items x and y can be used as x, y and x+y, which is 2^n-1=3 combinations. According to the Examiner's formula, the number would be $2x10^2$=200. The magnitude of the error in this regard grows exponentially with the number of markers added. So, if n=3, the number of possible combinations is 7, while according to the Examiner's formula, the number would be $2x10^3$=2000, or if n=4, the number of possible combinations is 15, while according to the Examiner's formula, the number would be $2x10^4$=20,000.

significantly associated with an increased risk of subclinical atherosclerosis, and that the risk increases when combined with other known atherosclerosis risk factors such as hypertension, diabetes, *etc.*, cannot be used clinically since "only 581 patients were confirmed as having an evidence of subclinical atherosclerosis... among 2733 patients, who showed subclinical atherosclerosis as measured by the presence/amount of MCP-1." Office Action, page 13.

Applicants respectfully submit that such assertions appear to be directed to the question of enablement, rather than to written description. Perhaps more importantly, such assertions, which indicate the Examiner's apparent belief that only "specific markers" (that is, markers that are only affected by a specific disease state) can be used in diagnostic methods, are not consistent with either the subject matter of the present claims, or the use of biomarkers generally in the art.

Applicants note that the present claims are not directed to diagnosis. The present claims are directed to risk stratification; that is, identifying an increased risk of subclinical atherosclerosis in a human subject. The present specification demonstrates that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Specification, Example 5. In this regard, MCP-1 may be used in a similar fashion to variables such as CRP, which exhibits similar odds ratios for identifying subclinical atherosclerosis as those seen in the present study for MCP-1. Compare Wang *et al., Arterioscler. Thromb. Vasc. Biol.* 22: 1662-67, 2002, table 3, and paragraphs [0255] and [0256] of the present specification. Such blood-based tests can be used to screen for those individuals at increased risk for future cardiovascular events. Applicants also note that Deo *et al., J. Am. Coll. Cardiol.* 44: 1812-18, 2004, published after the filing date of the present application, confirms the ability of MCP-1 to identify an increased risk of subclinical atherosclerosis in accordance with the present claims.

While one might desire to have available "specific markers" for a particular disease or condition that are elevated in every patient suffering from a disease, and only in those suffering from a disease, that is typically not possible. Fortunately, even nonspecific markers in the hands of the skilled artisan can be useful clinically, as the skilled artisan does not use diagnostic tests in an informational vacuum. Rather,

diagnostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject.

For example, CRP is a marker that is elevated in numerous inflammatory processes, including cancer, connective tissue disease, heart attack, infection, inflammatory bowel disease, lupus, pneumococcal pneumonia, rheumatoid arthritis, rheumatic fever, and tuberculosis. *See, e.g.*, http://www.nlm.nih.gov/medlineplus/ency/article/003356.htm. While only a fraction of subjects having an increased CRP level will have any one of these conditions, CRP tests are FDA approved and routinely used by clinicians. Similarly, D-dimer is an FDA-approved test used routinely by artisans in the evaluation of pulmonary embolism, but is not a specific marker of pulmonary embolism. *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000, page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the specificity of all DD assays is expected to be low"). This is not meant to be an exhaustive list, but rather is intended to point out that the state of the prior art plainly indicates that markers need not be elevated in a single specific condition for such markers to be useful to the artisan in clinical practice. Few, if any, such definitive tests exist.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* An adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a).

In the present case, the specification as filed adequately conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date.

See MPEP § 2163.02. Because the written description requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

6. 35 U.S.C. § 112, first paragraph (enablement)

Applicant respectfully traverses the rejection of claims 32-44 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The factors relevant to an enablement analysis are enumerated in *In re Wands*. Applicants attempt to address the Examiner's remarks in the context of the various *Wands* factors in the following remarks. Before doing so, however, Applicants wish to emphasize the following facts concerning the Examiner's comments regarding enablement.

The Examiner's rejection appears to be premised on the same assertions made in the written description rejection. For example, the Examiner repeats the assertions that because MCP-1 lacks specificity (Office Action, page 16) and that only a subset of subjects having an elevated MCP-1 level have subclinical atherosclerosis (Office Action, page 17). As noted above, the present claims are directed to risk stratification; that is, identifying an increased risk of subclinical atherosclerosis in a human subject; and the present specification demonstrates that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Specification, Example 5. The Examiner also repeats the comment that "the claims are not limited as to the number of markers," and the (vastly inflated) calculation concerning how many possible combinations of markers MCP-1 could take part in. Office Action, page 18. As noted above, claims written in "comprising" form never exclude additional unrecited elements or method steps, and so are always open to a literally infinite number of theoretical modifications and variations.

In addition, the Examiner refers to several publications in an attempt to paint the state of the prior art in a negative light. Many of these comments do not accurately represent the teachings of these publications. Furthermore, a recitation of difficulties that *might* be encountered in practice in the general use of biomarkers is not a sufficient basis

for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956); *Ex Parte Hicks*, 2000 WL 33673734 at *3.

A. The nature of the invention

The present invention is related to the use of biomarker measurements to identify a subject's risk of subclinical atherosclerosis. In particular, independent claim 32 refers to:

> A method of identifying an increased risk of subclinical atherosclerosis in a human subject, comprising
>
> performing an assay that detects monocyte chemoattractant protein-1 on a blood sample from said subject to provide a monocyte chemoattractant protein-1 assay result; and
>
> correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.

B. The state of the prior art

The state of the prior art is that biomarkers are routinely used in the art for diagnosis and prognosis of individual cardiac conditions.

With regard to traditional atherosclerosis risk factors, systolic blood pressure, blood glucose, and cigarette smoking had been reported as risk factors for subclinical atherosclerosis. Kuller et al., Am. J. Epidemiol. 139(12):1164-79, 1994. With regard to biochemical markers, CRP, LDL, and oxidized LDL had been reported to provide similar odds ratios as those seen in the present study for MCP-1. Wang *et al., Arterioscler. Thromb. Vasc. Biol.* 22: 1662-67, 2002, table 3. Hulthe and Fagerberg, *Arterioscler. Thromb. Vasc. Biol.* 22: 1162-67, 2002, abstract.

Applicants also note that, since the present application was filed, Deo *et al., J. Am. Coll. Cardiol.* 44: 1812-18, 2004, reported on the use of MCP-1 in identifying an increased risk of subclinical atherosclerosis, as described in the present claims. Additionally, Beloqui *et al., Eur. Heart J.* 26:153-58, 2005, reported on the use of monocyte cyclooxygenase-2 activity; Nelson *et al., Am. J. Epidemiol.* 163:903-12, 2006, reported on the use of sphingomyelin; Amar *et al., J. Hypertens.* 24:1083-88, 2006,

reported on the use of IL-6; and Orbe *et al., J. Thromb. Haemost.* 5: 91-7, 2007, reported on the use of matrix metalloproteinase-10; in each case as a risk marker for subclinical atherosclerosis. This list is exemplary only.

In contrast to the well established use of biomarkers in the art, the Examiner refers to several publications in an attempt to paint the state of the prior art in a negative light. Many of these comments amount to a recitation of difficulties that *might* be encountered in practice in the general use of biomarkers. That type of reasoning is not a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3. In addition, the Examiner's assertions about the limits of the prior art are not well founded.

For example, the Examiner states that Bast *et al., Clin. Cancer Res.* 11: 6103-8, 2005, "point to the 'lengthy process' of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically." Office Action, page 20. In addition to being merely a recitation of difficulties that *might* be encountered in practice, the Examiner has failed to acknowledge that this "lengthy process" quote, which is found on page 6105, right column, of Bast *et al.*, addresses why some marker tests do not obtain federal regulatory approval. It is not a requirement of the patent laws that a patent application be sufficient to obtain FDA approval, as "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled." See MPEP § 2164.05.

The Examiner also states that LaBaer, *J. Proteome Res.* 4: 1053-9, 2005, "teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting." Office Action, page 20. Again, this is nothing more than a recitation of difficulties that *might* be encountered in practice, and of basic considerations that the author believes should go into any biomarker discovery program. More appropriately, the LaBaer publication reflects considerations that are routine to one skilled in the field of biomarkers.

The Examiner further attempts to support the rejection (see paragraph bridging pages 20 and 21 of the Office Action) by reference to the following section from Baker, *Nature Biotechnology* 23: 297-304 (2005), page 298:

> Walking on Thin Ice
>
> 'Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is;' says Ole Vesterqvist, director of clinical discovery at NewYork-based Bristol-Myers Squibb. 'You start walking, and you get comfortable. Then you break through.' Vesterqvist describes an example in which published clinical data showed that people with heart failure had higher levels of the peptide endothelin I (ET-1) compared to healthy controls, based on immunoassays. But in studies at Bristol-Myers Squibb, these patients showed no increase in plasma concentration of the peptide, Eventually, Vesterqvist's group found research revealing that the previous studies used an antibody that cross-reacted with the precursor to ET-1, big-ET. Although levels of the precursor are higher in patients with heart failure, the levels of ET-1 are not. Ironically, the Bristol-Myers Squibb assay did not produce the expected results because it was more specific for ET-1 than assays previously used in other laboratories.

The discussion to which the Examiner refers is nothing more than an anecdotal report of a rather simple error on the part of one researcher in one example. To the extent the passage is meaningful at all, it speaks to the need for a rather basic understanding of the biomarker with which one is working.

Applicants respectfully submit that the state of the prior art is one of common usage of biomarkers generally, and that each of the publications cited by the Examiner are consistent with this understanding.

C. The relative level of skill in the art

The skill in the art is extremely high. The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients, and also has extensive experience in the generation and characterization of antibodies for use in such tests. As noted above with regard to the state of the art, the skilled artisan is well aware of the potential pitfalls that might be encountered in practice. The artisan is prepared to perform the necessary studies to practice the claimed methods, and understands that the required methods are routine in the art.

D. The quantity of experimentation necessary

The present claims do not relate to any new general methods for the analysis of biomarkers. Instead, the present invention lies in the discovery that elevations in MCP-1 levels indicate a significantly increased risk of subclinical atherosclerosis in a subject. Once MCP-1 has been identified, little is required of the skilled artisan in the way of experimentation to practice the invention.

In view of the teachings of the specification and the knowledge available in the art, the quantity of experimentation required to practice the invention is no more than routine. The specification provides the artisan with detailed examples of which markers to use and which cardiovascular disorders are to be distinguished. It further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis. When properly considered, it is apparent that what the Examiner likens to "tossing out the mere germ of an idea"(Office Action, page 18) is actually a complete description of how to make and use the claimed invention from start to finish.

E. The predictability of the art

In the present case, the methods to be followed are all routine; the only factor required to practice the claimed invention is the understanding that such methods should be pursued, an issue that is solved by reference to the present specification and claims.

The Examiner's comments in the Office Action regarding the state of the prior art (discussed above) are also relevant to an understanding of the predictability of the art. As discussed in detail above, assertions such as there can be a "lengthy process of assay development," that "many markers that correlate with disease statistically may not prove to be useful clinically," or that "the process of converting such a biomarker into a practical clinical test" amount to broad allegations that the disclosure is speculative, coupled with a recitation of difficulties that *might* be encountered in practice. Such reasoning, however, is legally insufficient for rejecting a claim under the enablement requirement.

Applicants respectfully submit that the test of enablement is not whether certain scenarios may be constructed in which the invention might not work, but rather whether one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. The present specification and claims meet this standard.

F. The amount of direction or guidance

The specification provides the artisan with substantial guidance for the use of MCP-1 in identifying subjects that are at an increased risk of having subclinical atherosclerosis. The specification further informs the artisan of suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis.

G. The presence or absence of working examples

The specification provides exemplary data for the use of MCP-1 in the claimed invention. The Examiner's belief to the contrary (Office Action, page 21: "the specification fails to teach that MCP-1 alone can be used to diagnose atherosclerosis in a subject") exhibits a failure to consider the data presented in the specification with the level of knowledge available in the art.

H. The breadth of the claims

The claims are circumscribed in their breadth, in that they refer to methods that comprise performing an assay that detects monocyte chemoattractant protein-1 on a blood sample from a human subject to provide a monocyte chemoattractant protein-1 assay result; and correlating the monocyte chemoattractant protein-1 assay result to the risk of the presence or absence of subclinical atherosclerosis in the subject.

The Examiner's focus on the possible number of subject-derived markers that may be used under the claims fails to consider that claims written in "comprising" form never exclude additional unrecited elements or method steps, and so are always open to a literally infinite number of theoretical modifications and variations. The fact that the claims are written in this open form cannot form the basis for questioning a presumptively enabling disclosure.

I. Conclusion

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods using nothing more that routine experimentation. The rejection fails to consider the knowledge available in the art, being based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that *might* be encountered in practice. As such, the rejection does not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g., In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956), *Ex Parte Hicks*, 2000 WL 33673734 at *3.

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

7. 35 U.S.C. § 112, second paragraph (definiteness)

Applicants respectfully traverse the rejection of claims 32-44 under 35 U.S.C. § 112, second paragraph, as allegedly failing to comply with the definiteness requirement.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). Recognizing that the English language is not always precise, the settled law has established that the essential inquiry in a definiteness analysis is whether the claims set out and circumscribe the claimed subject matter with reasonable particularity. *See, e.g.,* MPEP § 2173.02. Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan. When viewed in this light, a claim must reach the level of being "insolubly ambiguous" in order to be indefinite. See, e.g., *Scripps Research Institute v. Nemerson and Konigsberg*, 78 U.S.P.Q.2d 1019, 1030 (Bd. Pat. App & Interf. 2005).

A. The Examiner contends that claim 32 is allegedly indefinite because "the presence or amount" lacks antecedent basis. Applicants traverse this rejection.

As discussed in MPEP §2173.05(e), "the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. In particular, inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface." In the present case, the "presence or amount" of MCP-1 is an inherent component of the sample that may be determined, for example by performing an assay.

Nevertheless, in an effort to advance prosecution, Applicants have amended claim 32 to refer to performing an assay that detects MCP-1, thereby providing an MCP-1 assay result. Applicants respectfully submit that the amendment renders the rejection moot.

B. The Examiner contends that the correlating step in claim 32 is allegedly indefinite because the claims do not recite exactly how the correlation takes place. Office Action, page 22. Applicants traverse this rejection.

The Examiner is confusing breadth with definiteness. *See, e.g.*, MPEP §2173.04 ("Breadth is not Indefiniteness"). The plain English meaning of "correlate" is "to establish a relation between." The skilled artisan understands that there are numerous different methods by which assay results may be correlated to a risk of subclinical atherosclerosis in a patient. As such, the precise methods to be used are best left to the discretion of the skilled artisan, depending for example upon the level of sensitivity and specificity desired from the method.

For example, one or more particular "bins" (*e.g.*, the "quartile" analysis presented in Example 5 of the specification) might be used. In another alternative, a median value in diseased subjects might be used as a threshold. In yet another alternative, a level above that seen in a normal population might be used as a threshold.

Applicant respectfully submits that, because of its common understanding in the art, the term does not rise to the level of being insolubly ambiguous, and is therefore definite within the meaning of 35 U.S.C. § 112, second paragraph.

C. With regard to the Examiner's comments concerning the phrases "determining the presence or amount of monocyte chemoattractant protein-1 or a marker related thereto" in claim 32 and " determining the concentration of monocyte chemoattractant protein-1 or a marker related thereto" in claims 33, 34, and 40, Applicants do not fully understand the objections of the Examiner, as the meaning of the claims appears plain on their face. Nevertheless, in an effort to advance prosecution, Applicants have amended claims 32, 33, 34, and 40 to clarify the subject matter of the claims. Applicants respectfully submit that the amendment renders the rejection moot.

D. The Examiner contends that the term "a threshold concentration" in claim 33 is allegedly indefinite because the claims do not state a value for the threshold. Office Action, page 24. Applicants traverse this rejection.

Again, the Examiner is confusing breadth with definiteness. *See, e.g.*, MPEP §2173.04 ("Breadth is not Indefiniteness"). The claims plainly state that the threshold is used in the following manner: one compares the MCP-1 concentration to a threshold concentration, and a concentration less than the threshold concentration is indicative of a first risk of subclinical atherosclerosis and a concentration greater than said threshold concentration is indicative of a second risk of subclinical atherosclerosis. This is a common method for the use of diagnostic markers.

With regard to what a particular threshold value might be, the skilled artisan further understands that the particular value of a marker in a subject may likely be dependent upon the particular assay employed by the artisan. For example, in the case of cardiac troponin I, it has been reported in the literature that measurements using different commercial troponin I assays on identical specimens may differ in measured concentration by 100-fold. *See, e.g.*, Christenson *et al.*, "Standardization of Cardiac Troponin I Assays: Round Robin of Ten Candidate Reference Materials," *Clin. Chem.* 47: 431-37 (2001). Thus, a particular threshold is only meaningful for a particular assay

and a particular patient population. Determining a desired threshold for a marker such as MCP-1 is a straightforward determination performed simply by assaying the marker(s) in an appropriate subject population using the assay selected by the artisan, and selecting a threshold to provide a desired sensitivity and specificity. Such determinations are routine in the art, and are appropriately left to the skilled artisan.

Applicant respectfully submits that, because of its common understanding in the art, the term does not rise to the level of being insolubly ambiguous, and is therefore definite within the meaning of 35 U.S.C. § 112, second paragraph.

E. With regard to the Examiner's comments concerning claims 37-39, the claims are cancelled herein, rendering the rejection moot.

F. The Examiner contends that claim 40 is allegedly indefinite because "the presence or amount" lacks antecedent basis. Applicants traverse this rejection.

As discussed above, the "presence or amount" of MCP-1 is an inherent component of the sample that may be determined, for example by performing an assay. MPEP §2173.05(e) notes that "the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. In particular, inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface."

Nevertheless, in an effort to advance prosecution, Applicants have amended claim 40 to refer to performing an assay that detects MCP-1, thereby providing an MCP-1 assay result. Applicants respectfully submit that the amendment renders the rejection moot.

E. With regard to the Examiner's comments concerning claim 44, Applicants respectfully submit that the foregoing amendment renders the rejection moot.

8. 35 U.S.C. §102

The Examiner has rejected claims 32 and 42-44 under 35 U.S.C. § 102(b) as allegedly being anticipated by Parthasarathy *et al.*, US20020052000 (hereinafter "Parthasarathy"). Applicant respectfully traverses this rejection.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also MPEP §2131.

Parthasarathy discloses a method and kit "for the assessment of the state of lipid peroxidation of a host" and for "the identification and quantification of inflammatory disorders." *See, e.g.*, Parthasarathy, paragraphs [0013]-[0017] and [0020]. Concerning MCP-1, which is the subject of the present invention, Parthasarathy discloses that it is a "surrogate marker" of some unspecified inflammatory disease, of which "a cardiovascular disorder" is but one example. Parthasarathy, paragraphs [0097] and [0138]. It is also suggested that lipid peroxide forms of MCP-1 "may represent a sensitive and specific marker for lipid peroxide mediated vascular inflammatory events characteristic of atherosclerosis. Parthasarathy, paragraph [0098], emphasis added.

Importantly, Parthasarathy does not indicate that MCP-1 can be used to identify an increased risk of subclinical atherosclerosis, nor is there any exemplary data of any kind in Parthasarathy concerning detection of atherosclerosis at all. The claimed use of MCP-1 to aid in the early identification and treatment of those with subclinical atherosclerosis, demonstrated in the present specification in Example 5, is not disclosed in Parthasarathy.

Because Parthasarathy does not disclose each and every element of the present claims, Applicants respectfully submit that no *prima facie* case of anticipation has been established. Applicants, therefore, request that the rejection be reconsidered and withdrawn.

9. 35 U.S.C. §103

The Examiner has also rejected claim 34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Parthasarathy in view of Adelman *et al.*, U.S. Patent No.

5,482,935; and claims 40 and 41 as allegedly being unpatentable over Parthasarathy in view of Carville *et al.*, *Clin. Chem.* 42: 1537-41, 1996. Applicant respectfully traverses these rejections.

Each of these rejections relies on Parthasarathy as the primary reference. But, as discussed above, this ability of MCP-1 to aid in the early identification and treatment of those with subclinical atherosclerosis, which is the subject of the present claims, is not disclosed in Parthasarathy.

Moreover, Parthasarathy discloses a non-limiting list of "surrogate markers," of which MCP-1 is but one marker, indicating that these are markers for some unspecified inflammatory disease, of which "a cardiovascular disorder" is but one example. Parthasarathy , paragraphs [0097] and [0138]. Parthasarathy suggests that lipid peroxide forms of MCP-1 and these other markers "may represent a sensitive and specific marker for lipid peroxide mediated vascular inflammatory events characteristic of atherosclerosis." Parthasarathy, paragraph [0098], emphasis added. This suggestion is nothing more than an invitation "to explore a new technology or general approach that seemed to be a promising field of experimentation." At best, Parthasarathy suggests that MCP-1 may be "obvious to try," a rationale that does not support a *prima facie* case of obviousness. MPEP § 2145(X)(B). Additionally, it still requires a further leap to extend this suggestion by modifying it to arrive at the claimed use of MCP-1 to identify an increased risk of subclinical atherosclerosis.

Because the cited publications, considered alone or together, do not disclose or suggest each and every element of the claims, and because no motivation has been established to either combine or modify the cited publications to arrive at the claimed invention, Applicants respectfully submit that no *prima facie* case of obviousness has been established. Applicants, therefore, request that the rejections be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited.

Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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